A Phase 1a, Randomized, Placebo-controlled, Single & Multiple Dose-Escalation Study to Evaluate the Safety & Tolerability of Novel Regenerative Therapeutic NNI-362

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BACKGROUND: NNI-362 is a new chemical entity discovered through a phenotypic assay to identify small molecules that promote new neurons from human neural progenitor cells. Preclinical efficacy and safety studies supported a first-in-human testing in a healthy aged population. A placebo-controlled study allowed the determination of safety and tolerability, as well as secondary pharmacokinetics of two distinct NNI-362 formulations.

OBJECTIVES: The aim of this study was to determine the safety and tolerability of NNI-362 in a first-in-human study.

METHODS: NNI-362 was formulated by Parexel (Glendale, CA) as an aqueous suspension or lipid suspension. Individuals were enrolled in a placebo-controlled study with a 1:3 ratio of placebo:drug. The dosing in SAD cohorts was 10, 20, 60, and 120 mg and MAD cohort at 20 mg and a SAD/MAD at 120 and 240 mg, all under fasted conditions. Direct SAD and MAD pharmacokinetics were assessed at the two highest doses. A total of 56 subjects ages 50 to 72 were randomized to intervention or placebo, with the sponsor, PI, and subjects all blinded.

INTRODUCTION NNI-362*, a NCE, was discovered* through a phenotypic screen to identify neuron generation and neuroprotection capacity from human neural progenitors (Sumien et al., Stem Cell Res. & Ther. 12:59, 2021). NNI-362's unique MOA allosterically targets S6 kinase downstream of mTOR, that selectively stimulates translation in neural progenitor cells and promotes maturation of new neurons in aging and progressive disorders. Preclinical efficacy and safety was demonstrated prior to start of Phase1a clinical testing in an aged population (supported by NIA 1RO1 AG056561, PI: JK-A). Safety and tolerability of oral NNI-362 were the primary readouts. Secondary pharmacokinetic readouts involved two liquid formulations - the first being aqueous liquid in Cohorts A-E and the second being a lipid based liquid in Cohorts F and G.
Planned studies will include plasma levels of phosphoTau181 pre and post treatment in MAD Cohort 240 mg to determine potential differences with NNI-362 treatment in aged subjects (Mayo Laboratories). Further preclinical analysis of NNI-362 in an rat AAV-alpha synuclein model of Parkinson's disease showed behavioral benefit including reversal of anosmia (J Kelleher-Andersson manuscript in preparation) with immunohistochemical analysis of neuron regeneration still in progress (MOTAC, France). Long-term GLP safety in rats and dogs for 6 and 9 months, respectively, will need to be completed prior to POC trials. Proposed POC trial designs with lipid-based formulated NNI-362 for mild to moderate Alzheimer's disease and for early Parkinson's disease are provided.

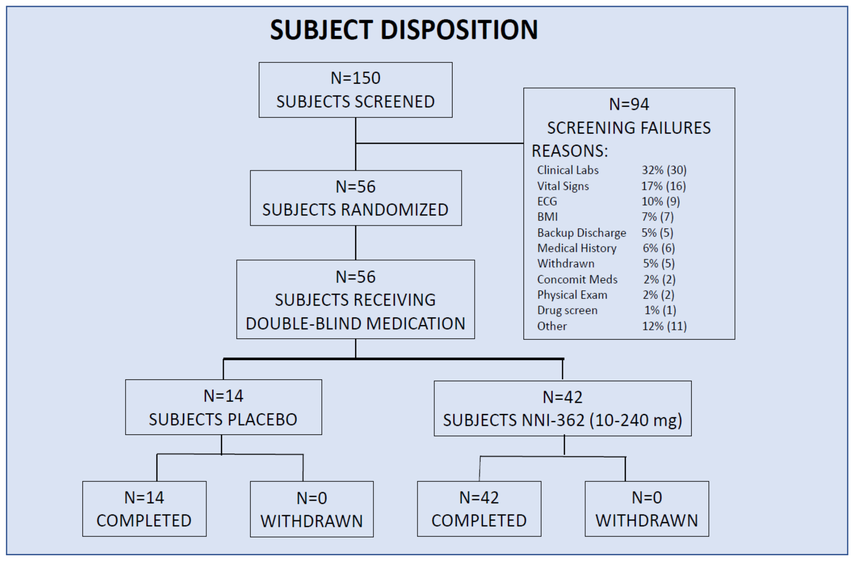

Table 1	Placebo (n=14)	NNI-362 (n=42)
Male	5 (36%)	18 (43%)
Age (yrs)	59.6 ± 5.4	59.6 ± 5.5

Table 2	Asian	Black or African-American	White	Other	Total
Female	10	5	18	0	33
Male	2	3	16	2	23
Total	12	8	34	2	56

Table 3	Hispanic or Latino	Not Hispanic or Latino	Unknown	Total
Female	6	26	1	33
Male	3	20	0	23
Total	9	46	1	56

Table 4	Avg Age	Total
Female	60.1 ± 5.3	33
Male	59.0 ± 5.8	23
Total	59.6 ± 5.5	56

A Proposed Study of NNI-362 in Early Parkinson's Patients

Study Type	**Interventional, Phase 1b/2a**
Study Design	**Randomized, Intervention Model: Parallel Assignment**
Masking	**Triple (Participant, Care Provider, Investigator)**
Study Design	**Randomized, Intervention Model: Parallel Assignment** **Masking: Double (Participant, Investigator)**
Conditions	**Parkinson's Disease (Age 40-72)**
Interventions:	**Drug: NNI-362 oral liquid-gel cap Other: Placebo**
Enrollment	**75 (no controls), Male and Female**
Endpoints	**1º - Safety and Tolerability, compare to baseline vMRI hippocampus** **2º - OLFACT™ Test Battery or UPSIT, MDS-UPDRS, MADRS-2, PDQ-39**

Arm	**Intervention/Treatment**
Experimental : NNI-362 oral liquid NNI-362 will be administered orally in the double-blind treatment over 6 months	**Drug**: NNI-362 oral liquid 120 mg **Drug**: NNI-362 oral liquid 240 mg
Placebo Comparator: Placebo will be administered orally in the double-blind treatment over 6 months	**Drug**: Placebo Participants will receive Placebo oral liquid daily for 6 months

A Proposed Study of NNI-362 in Mild to Moderate Alzheimer's Patients

Study Type	**Interventional, Phase 1b/2a**
Study Design	**Randomized, Intervention Model: Parallel Assignment**
Masking	**Triple (Participant, Care Provider, Investigator)**
Conditions	**Alzheimer's disease (Age 60-86)**
Interventions:	**Drug: NNI-362 oral liquid-gel cap Other: Placebo**
Enrollment	**105 (no controls), Male and Female (≥50% F)**
Endpoints	**1º - Safety and Tolerability, compare to baseline vMRI hippocampus** **2º - OLFACT™ Test Battery or UPSIT, ADAS-cog., Mini Mental State Examination (MMSE), ADCS-ADL, Plasma-PhosphoTau,**

Arm	**Intervention/Treatment**
Experimental : NNI-362 oral liquid NNI-362 will be administered orally in the double-blind treatment over 6 months	**Drug**: NNI-362 oral liquid 120 mg oral liquid daily for six months **Drug**: NNI-362 oral liquid 240 mg oral liquid daily for six months
Placebo Comparator: Placebo will be administered orally in the double-blind treatment over 6 months	**Drug**: Placebo Participants will receive Placebo oral liquid daily for 6 months

Efficacious Dose Level Potentially Met at Highest Human Oral Dose (240 mg)

- **Safety/Efficacy Model Male/Female Sprague-Dawley Rats**

- **10 mg/kg, po (lipid formulation) showed behavioral efficacy in a rat AAV-alpha synuclein model (both motor and anosmia)**
(*J. Kelleher-Andersson, manuscript in preparation*)

- **AUC at 10 mg/kg in rat is approximately equal to the AUC at 240 mg in humans, when considering a 20-fold protein binding ratio from rat to human**

- **Cmax at 10 mg/kg in rats approximately 2-fold Cmax at 240 mg in humans, when considering a 20-fold protein binding ratio from rat to human**

- **$T_{1/2}$ in humans at 120 & 240 mg = 12 hrs (~6 hrs in rat)**

- **No safety concerns in either rat or human (no dose dependent AEs, see Table 5)**

Table 5. Adverse Events

AE Category (All of Mild Grade)	SAD 10 mg		SAD 20 mg		SAD 60 mg		SAD 120 mg		MAD 20 mg		SAD+MAD 120 mg#		SAD+MAD 240 mg#			
	Placebo (n=2)	NNI-362 (n=6)	Placebo (n=2)	NNI-362 (n=6)	Placebo (n=2)	NNI-362 (n=6)	Placebo (n=2)	NNI-362 (n=6)	Placebo (n=2)	NNI-362 (n=6)	Placebo (n=2)	NNI-362 (n=6)	Placebo (n=2)	NNI-362 (n=6)	Placebo (n=14)	NNI-362 (n=42)
Eye Disorders[1]		1 (17%) UL									1 (50%)				1	1
Gastrointestinal Disorders[2]				1 (17%) U	2 (50%)					1 (17%)	3 (50%) U UL	1 (17%)	2 (50%)	1 (17%)	7	4
Nervous System Disorders[3]				1 (17%)	1 (50%)				1 (50%)	1 (17%)	2 (100%)		2 (50%)	1 (17%)	6	3
Respiratory, thoracic and mediastinal[4]										1 (17%) UL						1
Psychiatric[5]											2 (50%)			1 (17%)	2	1
Cardiac Disorders[6]														1 (17%) UL		1
Injury poisoning/procedural complications[7]												2 (33%) U U				2
Genl Disorders and Administrative sites[8]											1 (50%)	2 (33%) U		1 (17%)	1	3
Musculoskeletal and connective tissue[9]										1 (17%) U						1
															17	17
Pre-lock Definition																
U=Unrelated				1						1	1	3				
UL=Unlikely		1								1	1			1		
Possibly Treatment Related															15	9
# Oral Lipid Formulation																

[1]Eye redness, conjunctivitis; [2]Diarrhea, constipation, nausea, emesis, borborygmi, discolored feces; [3]Headache, dizziness, light headed, somnolence; [4]Sinus discomfort; [5]Abnormal dreams, insomnia; [6]Bigeminy-asymptomatic; [7]Laceration, thermal burn; [8]Feeling calm, somber, catheter site pain, foggy; [9]Back pain

Conclusions: Oral NNI-362 appears to be safe and well tolerated at doses up to 240 mg. A maximum tolerated dose (MTD) was not reached in this healthy aged population. The liquid-lipid formulation of NNI-362 at 120 and 240 mg revealed an increased C_{max} and AUC_{last} but no increase in AEs.
These data support a proof-of-concept trial of oral NNI-362 in individuals with Alzheimer's disease and other neurodegenerative disorders of aging associated with neuronal loss.